Liver Transplantation

November 25, 2003

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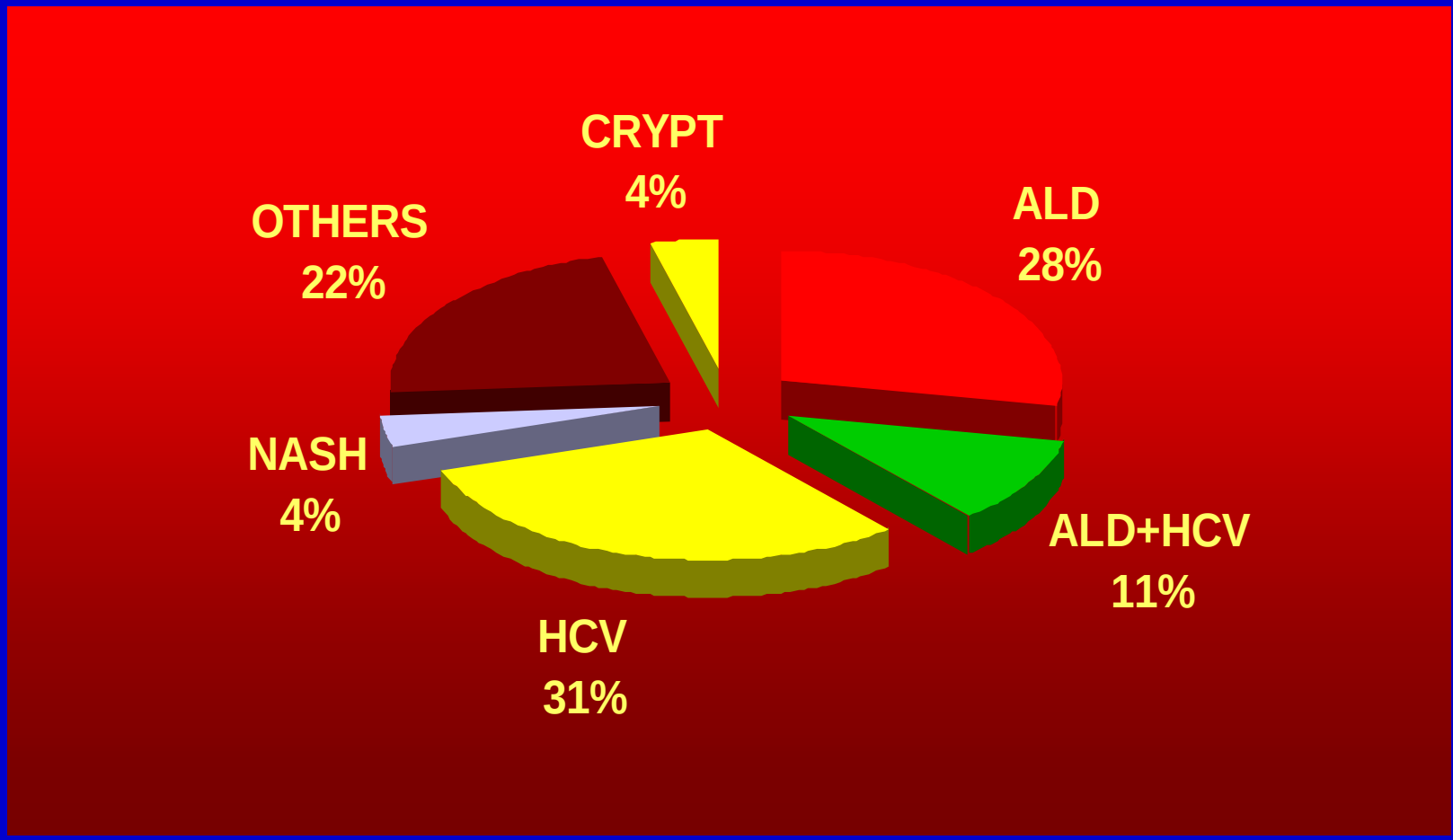
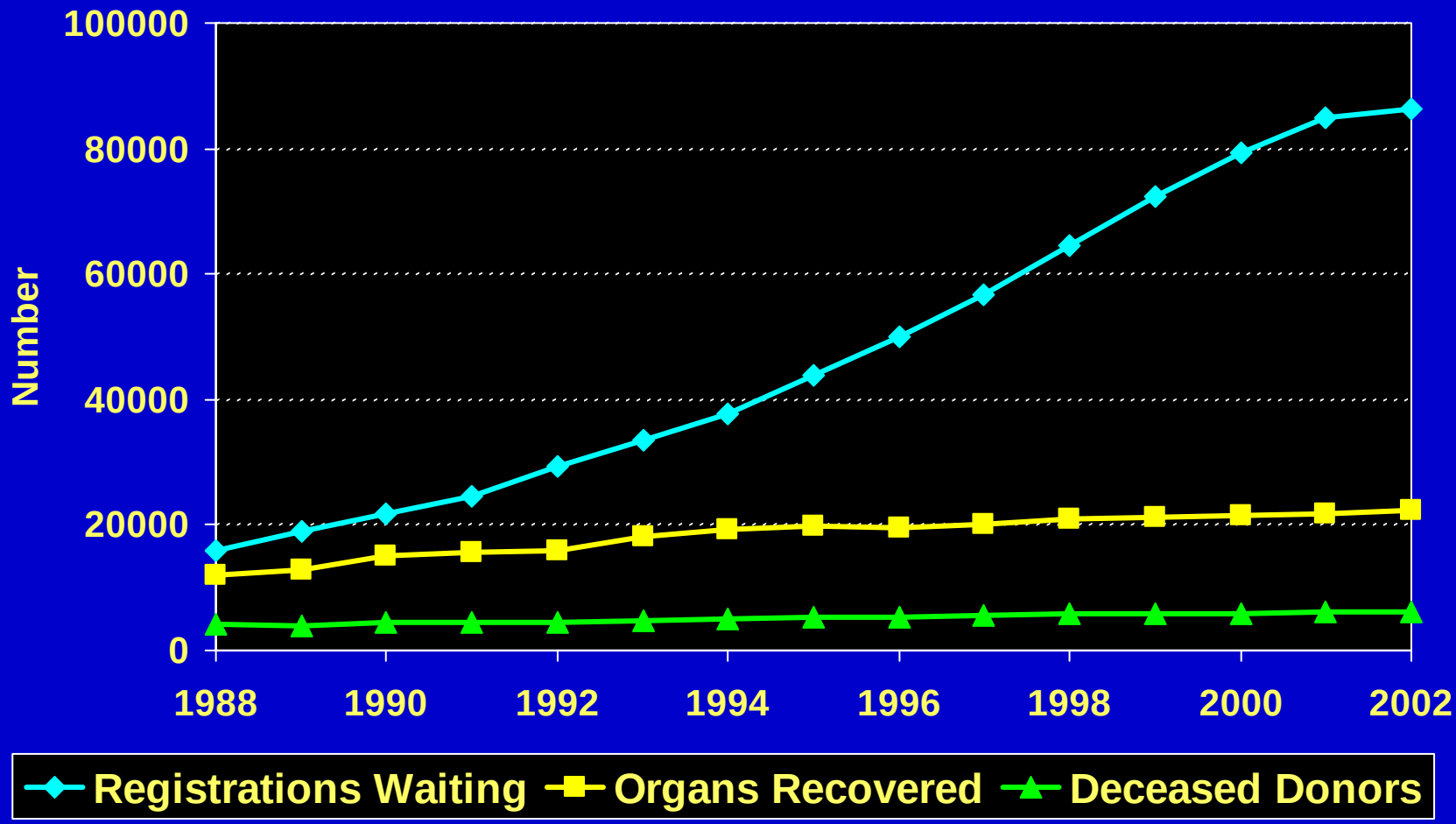
UW Hepatology Clinic/Hepatology inpatient Service
Jan 1994 - Dec 2001



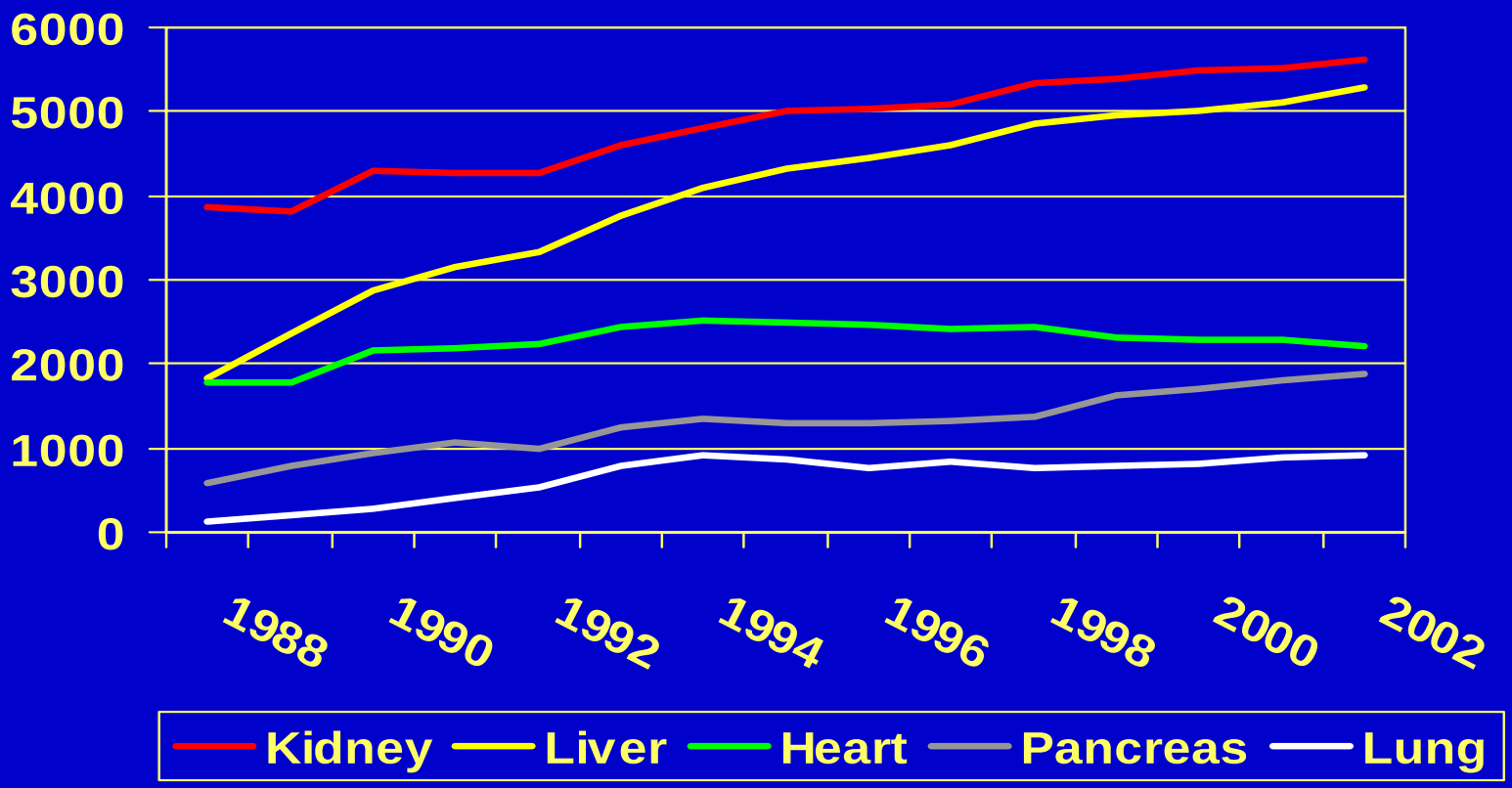
1664 patients with Chronic Liver Disease

- **Trends in organ donation**
- **Trends is in the waiting list**
- **Trends in allocation**
- **Outcome after liver transplantation**
- **Trends in immunosuppression**
- **Specific indications:**
- **Post transplant management:**
- **Research opportunities**

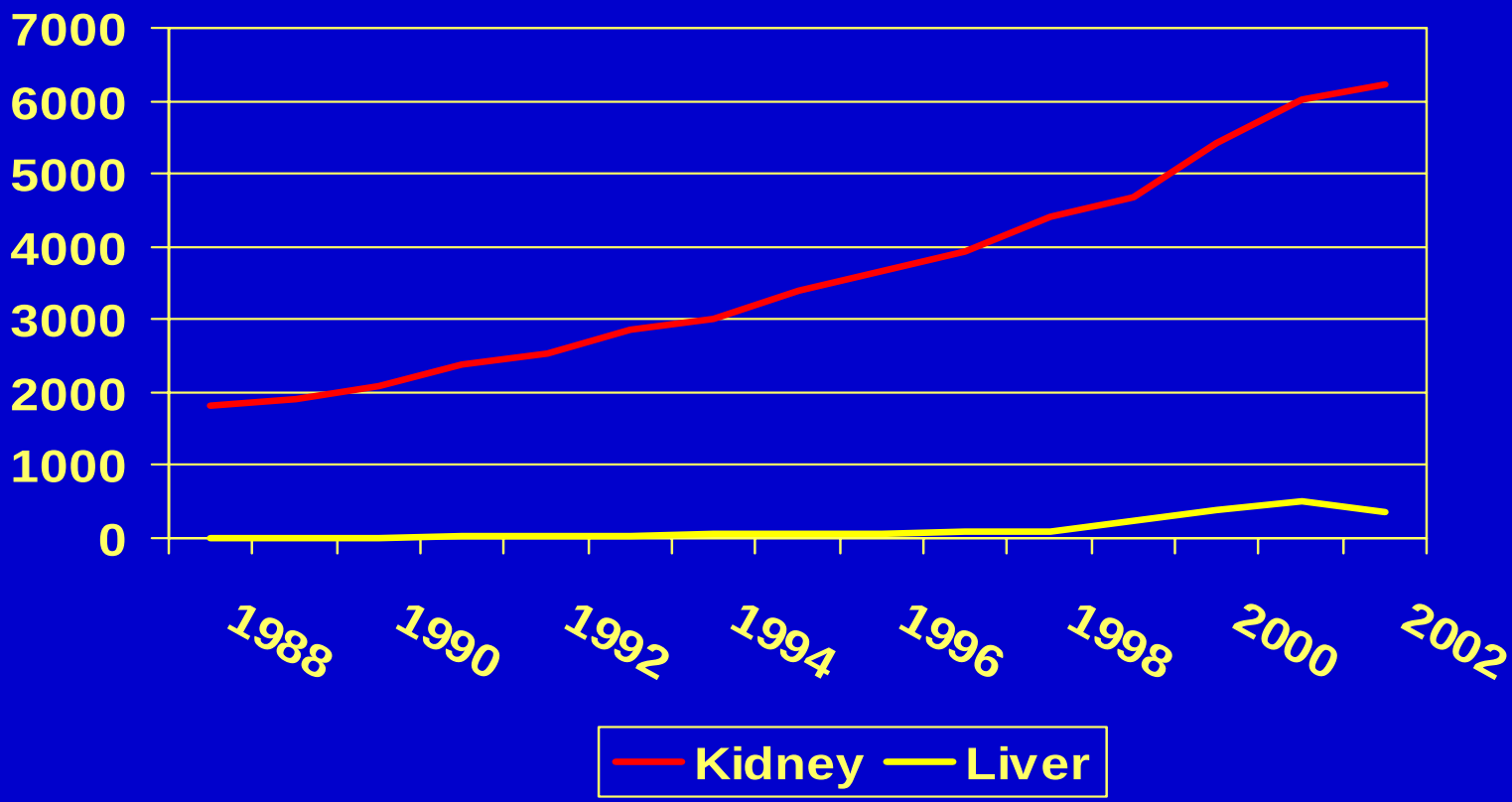
The U. S. Organ Shortage



TRENDS IN SOLID ORGAN DONATION: Deceased Donors



TRENDS IN SOLID ORGAN DONATION: Living Donors



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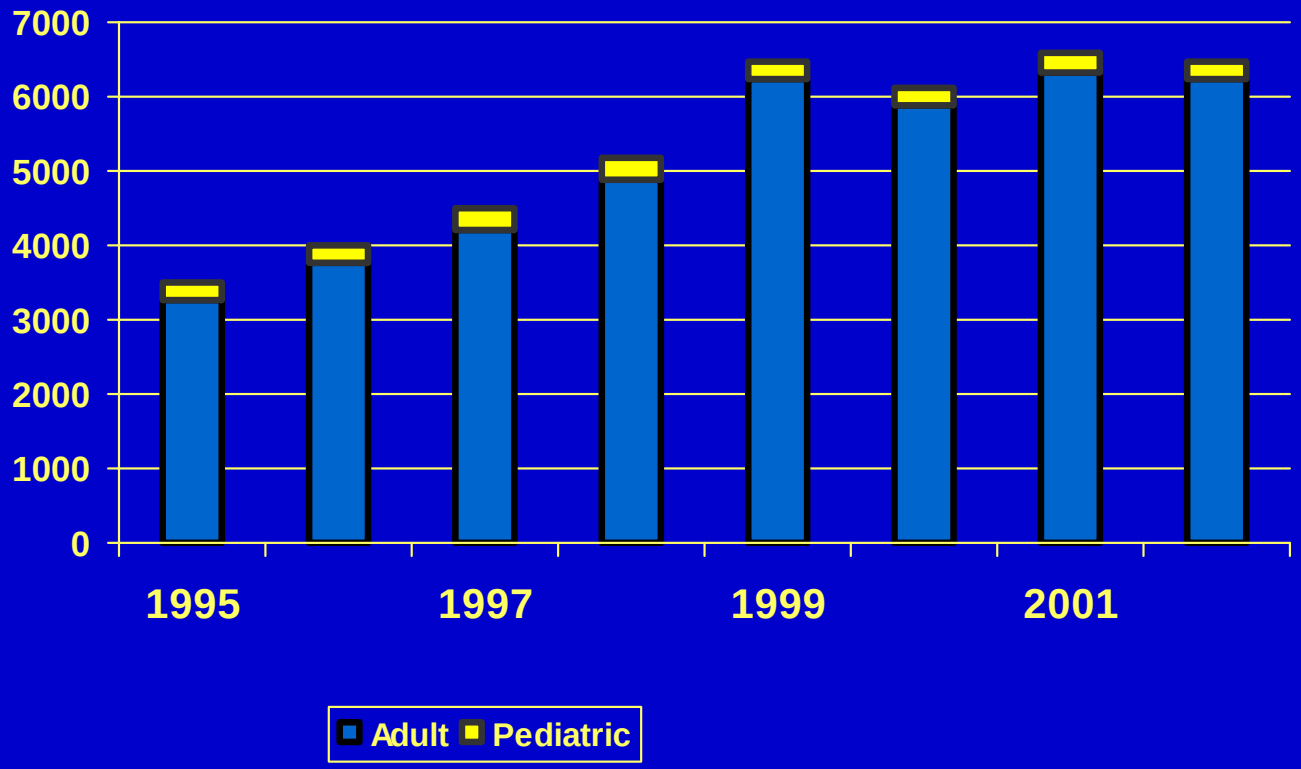
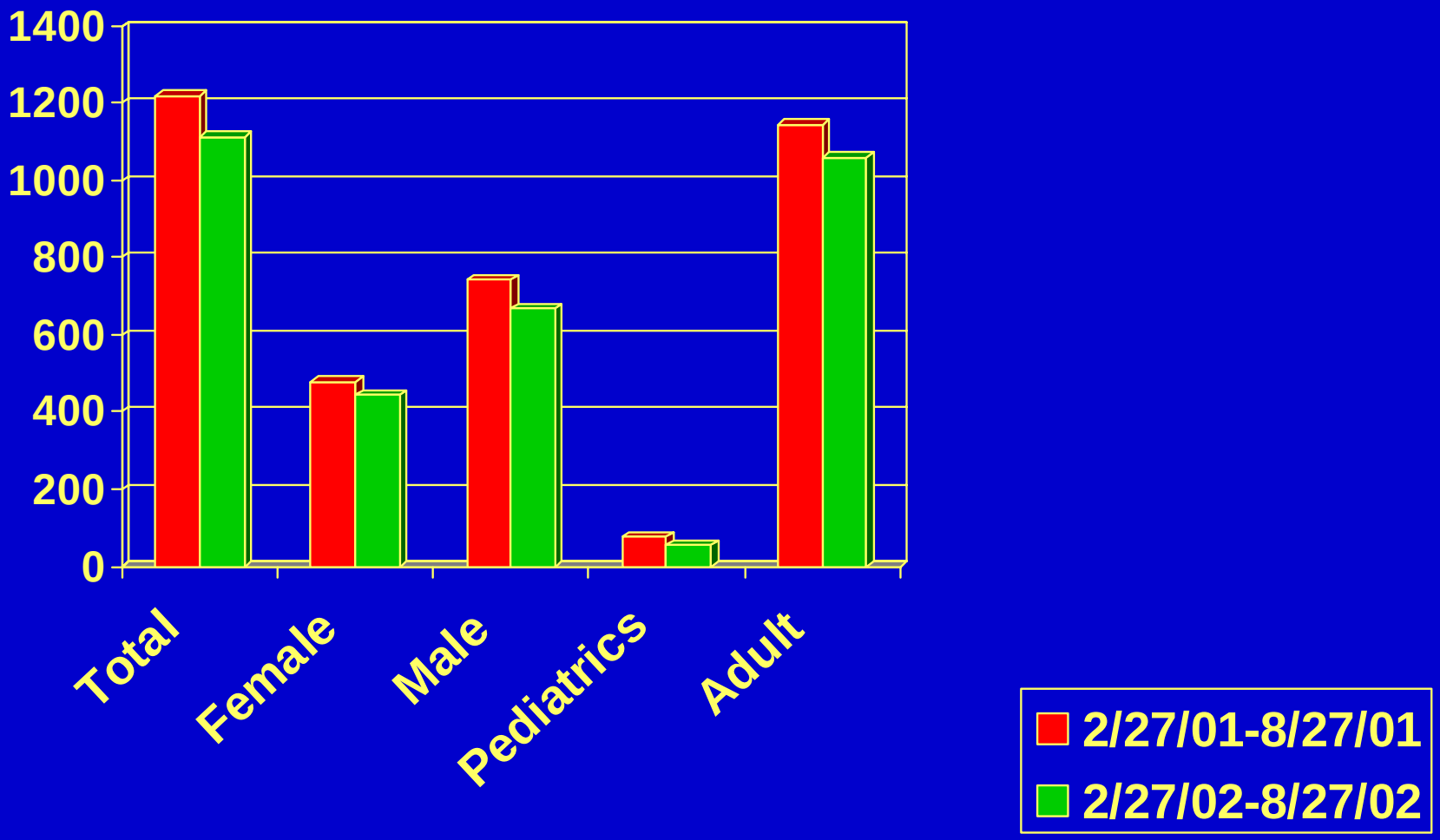
NATIONAL WAITING LIST
As of August 22, 2003

DEATHS ON THE NATIONAL WAITING LIST 1995-2002



Removals (Death or Too ill) from Waiting List Before and After MELD



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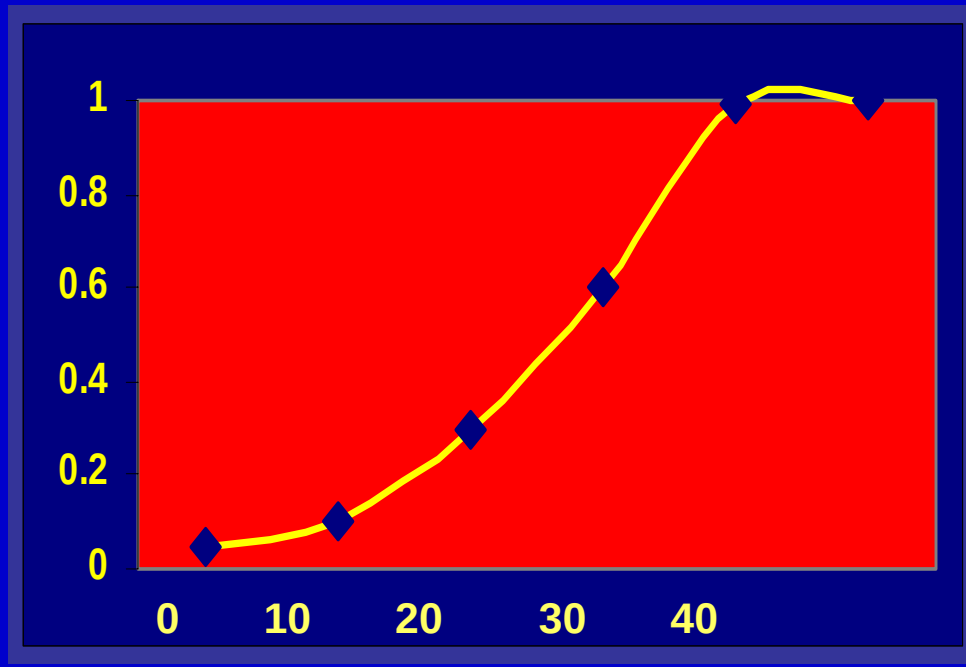
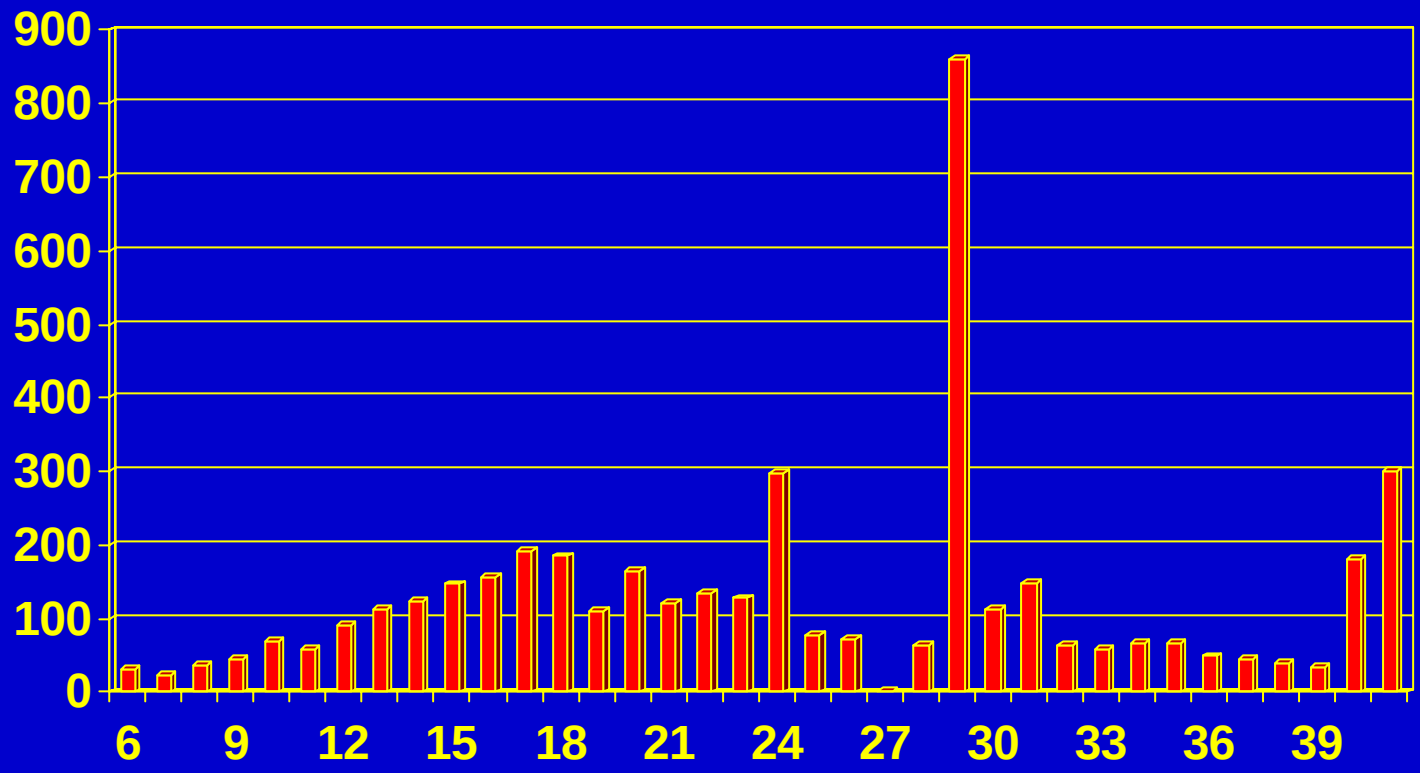
Model for End-stage Liver Disease (MELD) and Liver Allocation

- Introduced 2/28/02
- Objective parameters only:
  - Serum Bilirubin,
  - INR
  - Se Creatinine
- No ceiling effect
- Continuous thereby reducing the effect of waiting time on allocation
- HCC arbitrarily given MELD points

Relationship between MELD score and estimated 3-month mortality in chronic liver disease patients



Adult Liver Transplants February 28, 2002 - February 28, 2003



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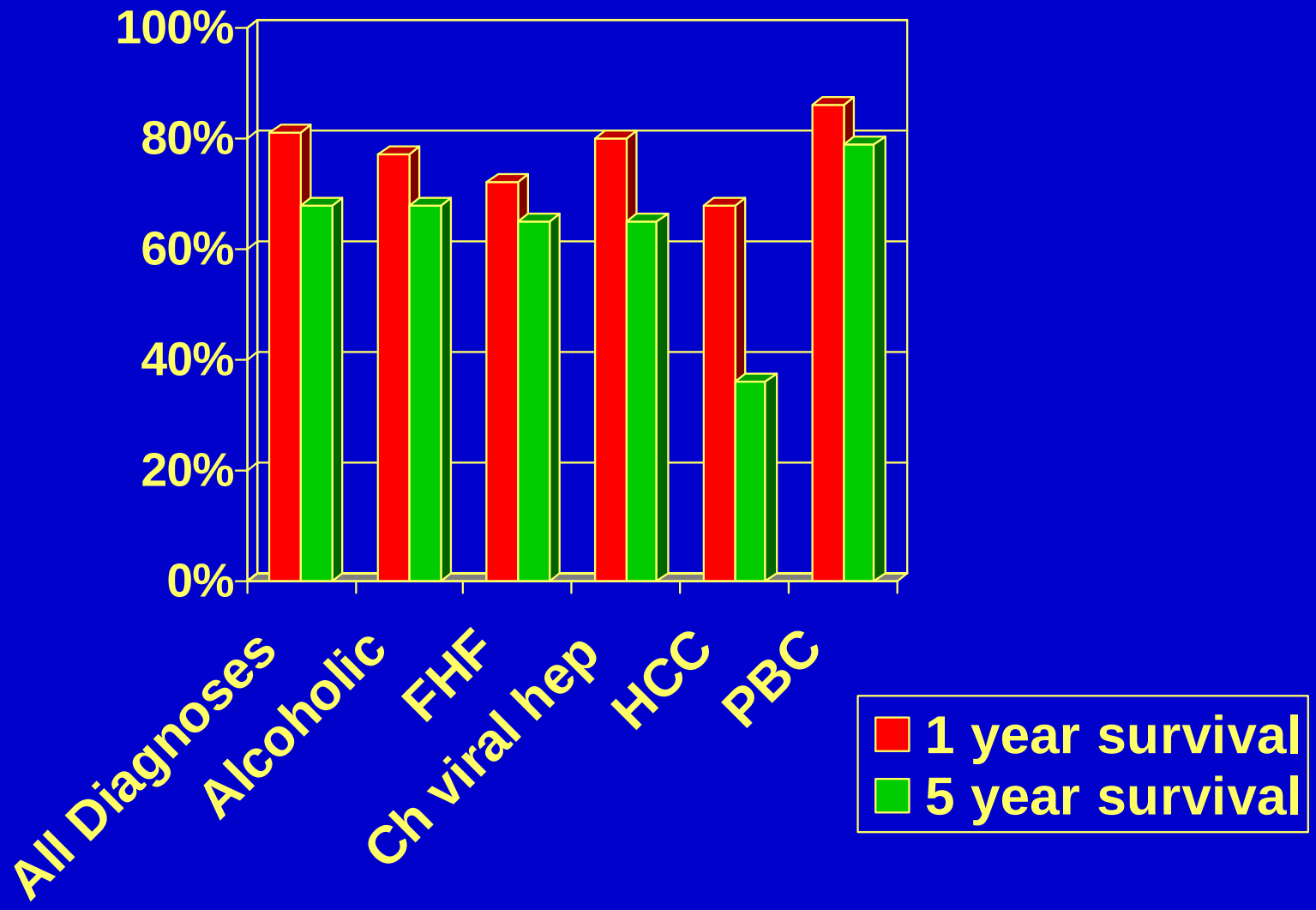
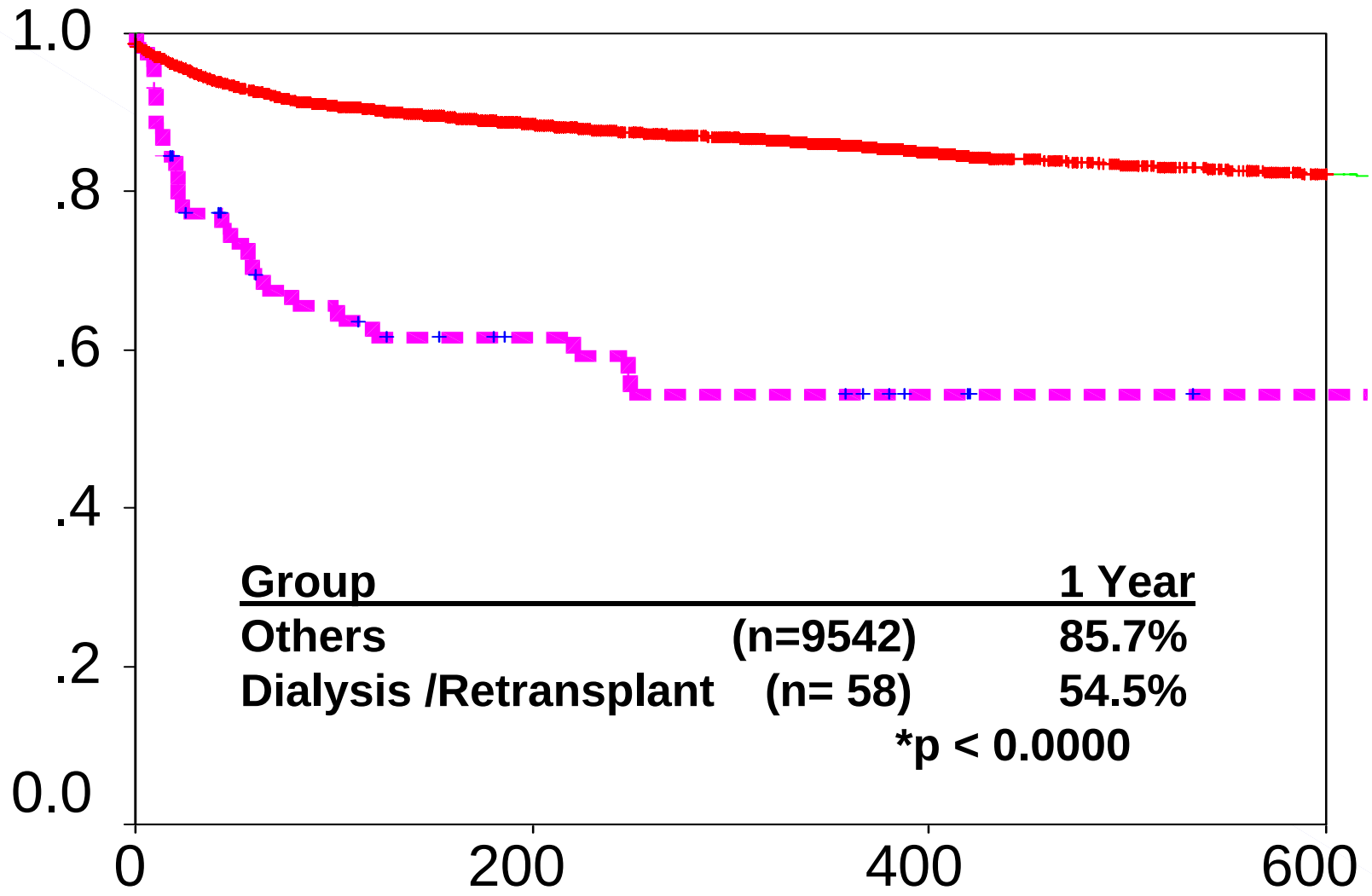
Survival after Liver Transplantation
UNOS Database (N = 14,771)

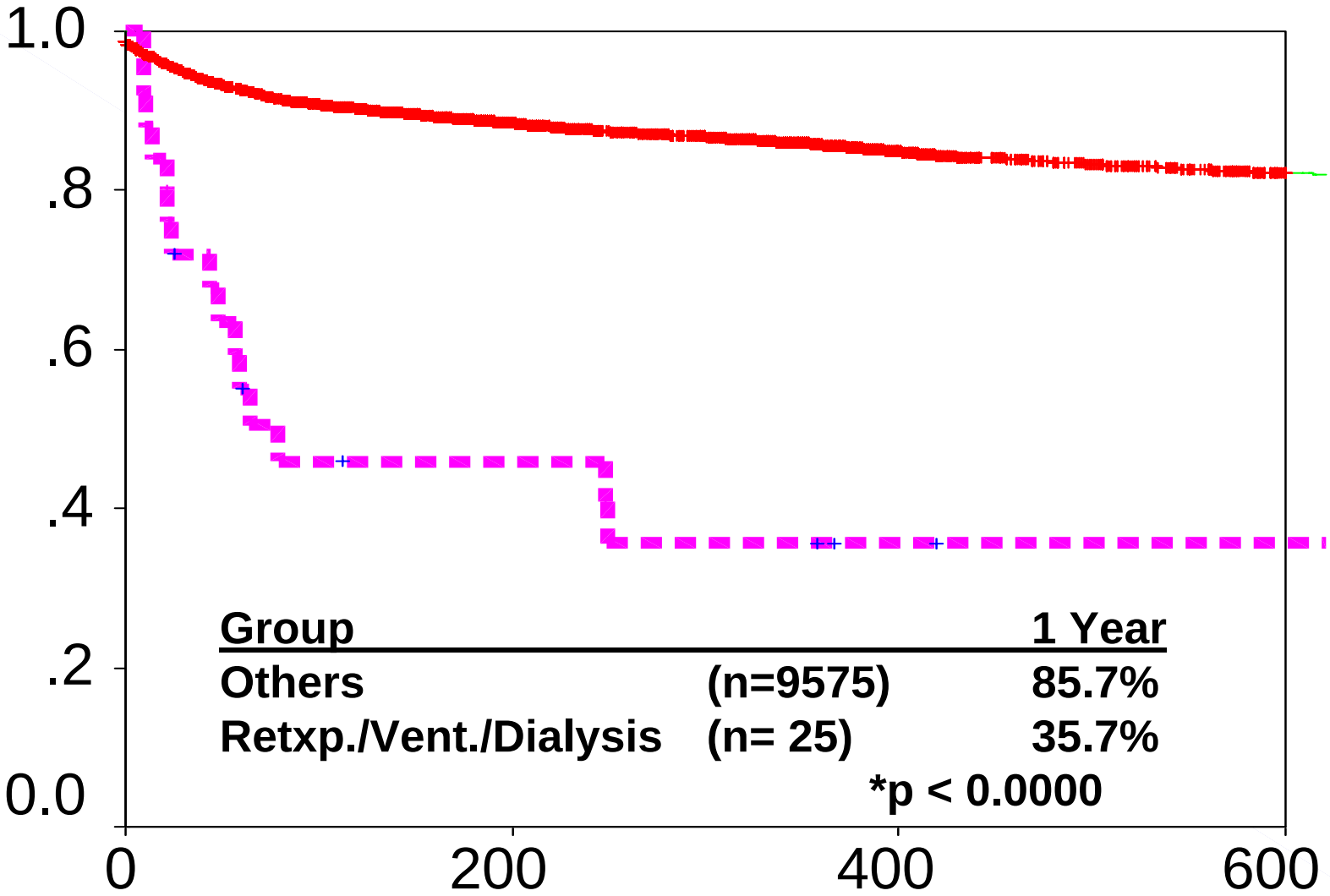


Patient Survival in Retransplanted & Primary Recipients



Markmann J et al. Transplantation 2003 (in press)

Patient Survival in Retransplanted & Primary Recipients

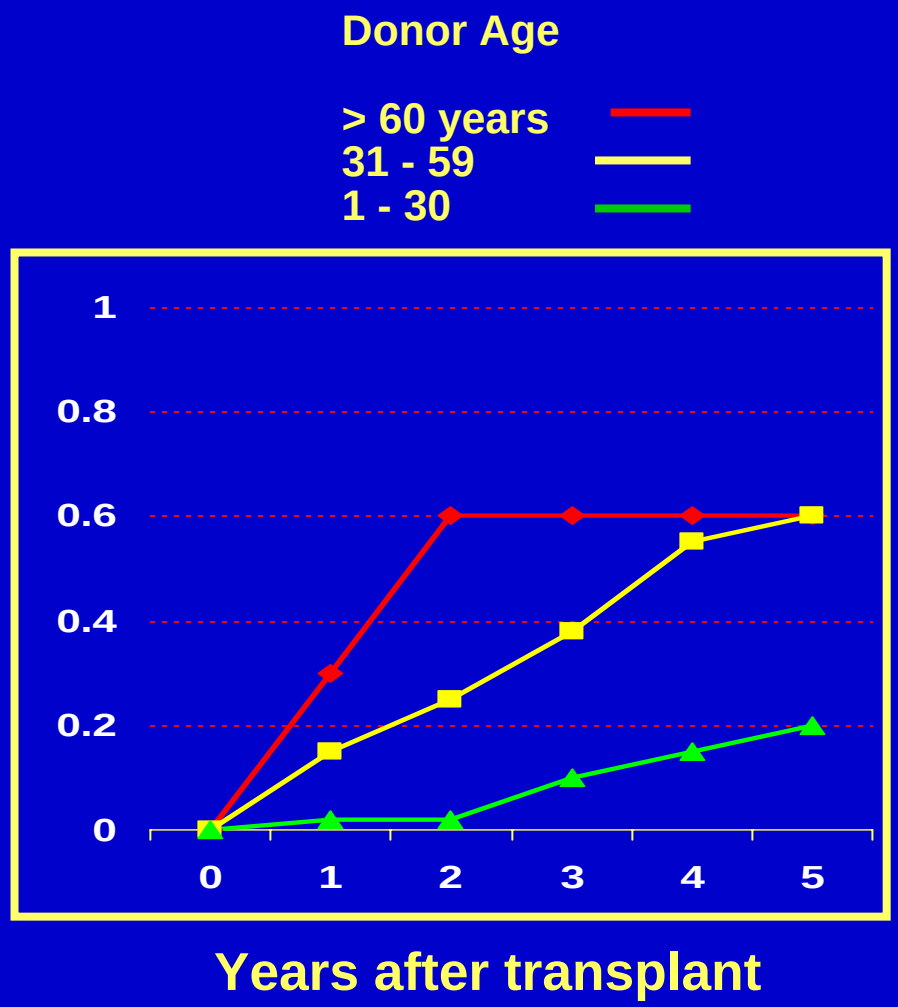


Markmann J et al. Transplantation 2003 (in press)

Matching Donor to Recipient

- Spain has increased solid organ donation, especially by using donors > 45 years
- More rapid fibrogenesis within a HCV-infected cohort of recently transplanted liver recipients v. HCV-infected patients transplanted in earlier eras
- Hypothesis: older livers are more susceptible to HCV induced fibrogenesis

Berenguer M.et al. Hepatology. 2002; 36:202-10



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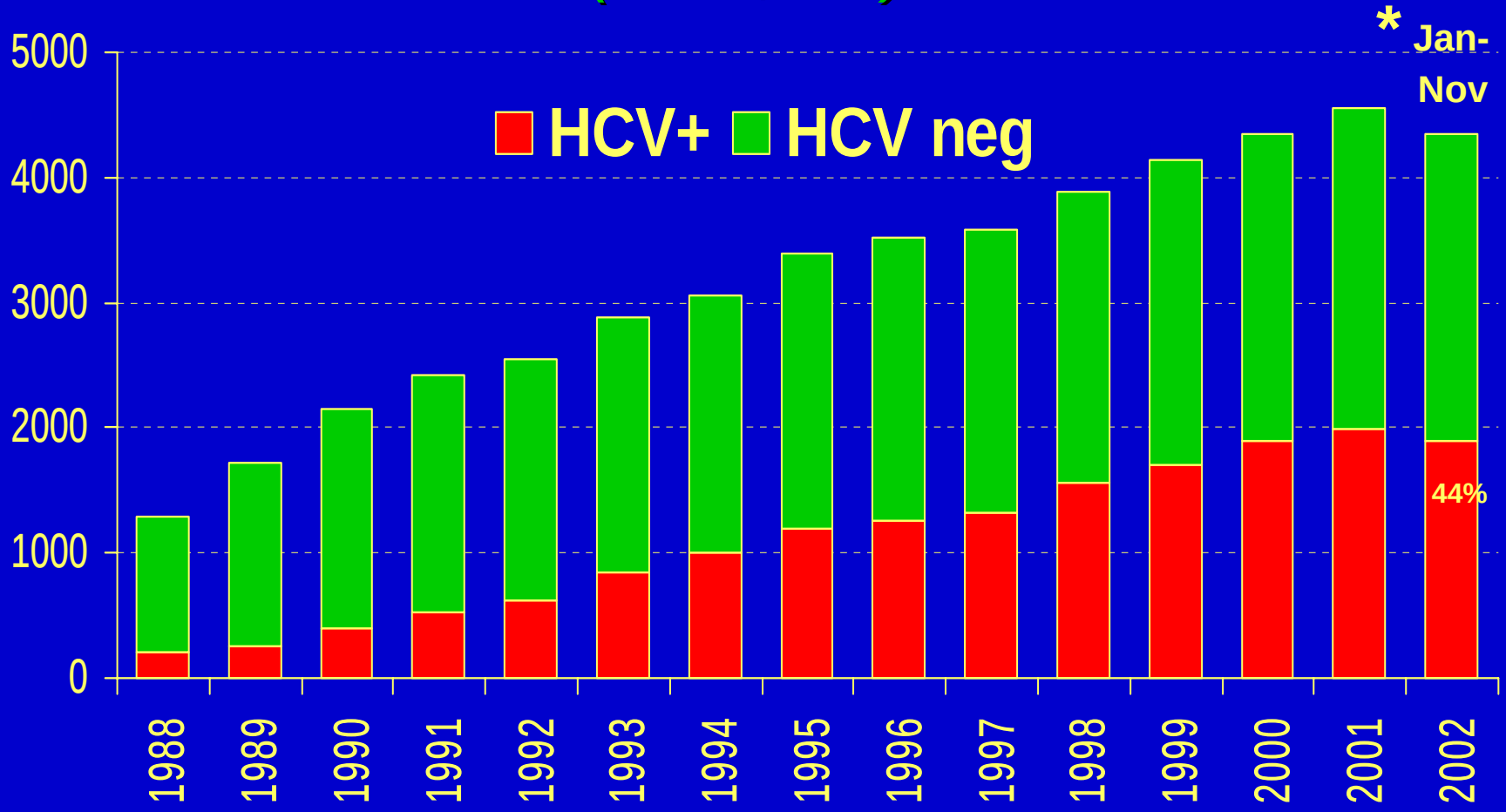
Liver Transplantation for HCV

U.S. Adult Liver Transplants 1988-2002

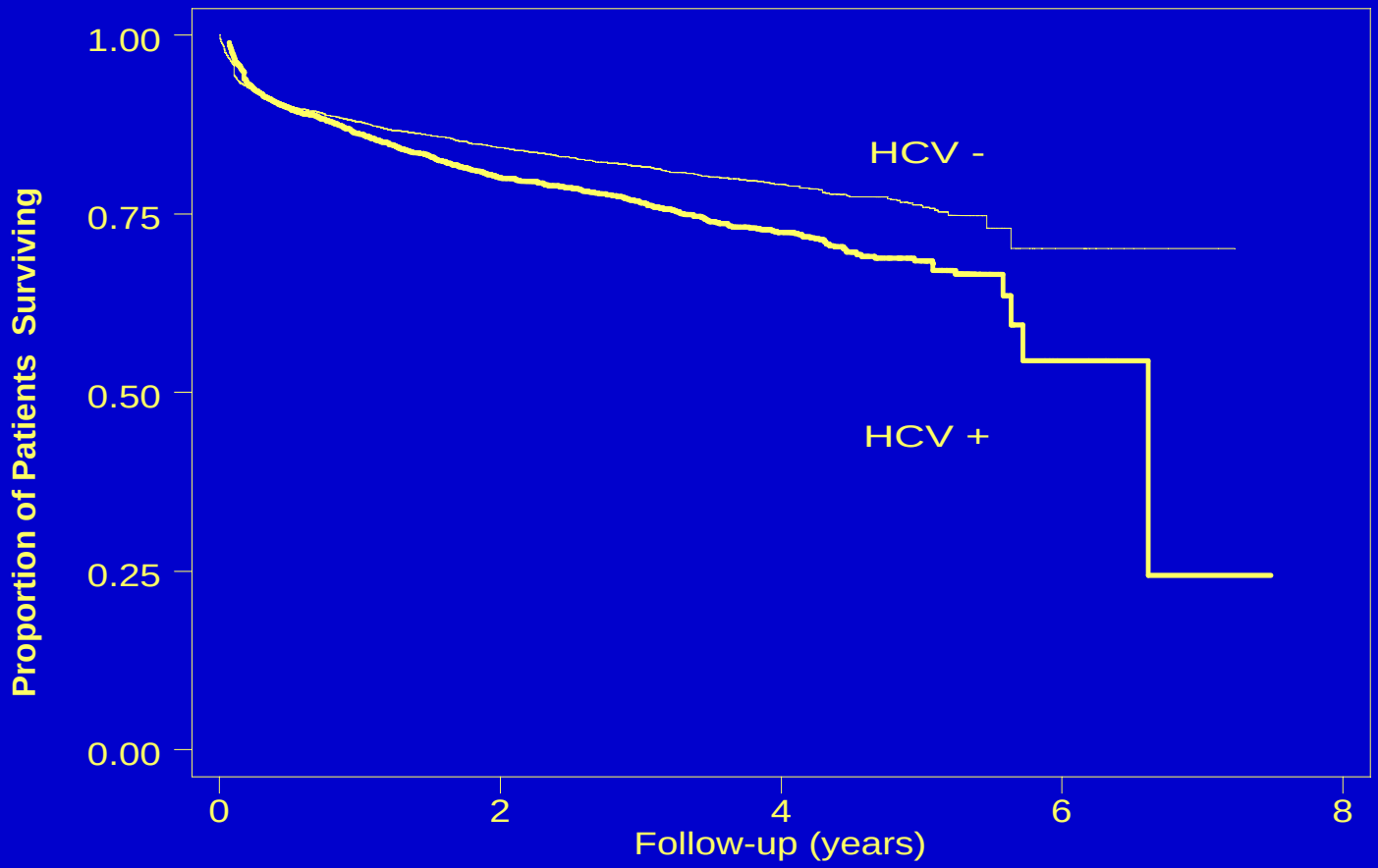
(n=47,881)



OPTN,2003

Patient Survival

UNOS Database. N=11,036; Forman et al, Gastro. 2002



	1 yr	3 yr	5 yr
HCV+	86.4%	77.8%	69.9%
HCV-	87.5%	81.8%	76.6%

Log rank x^2 = 19.7
P = 0.0001

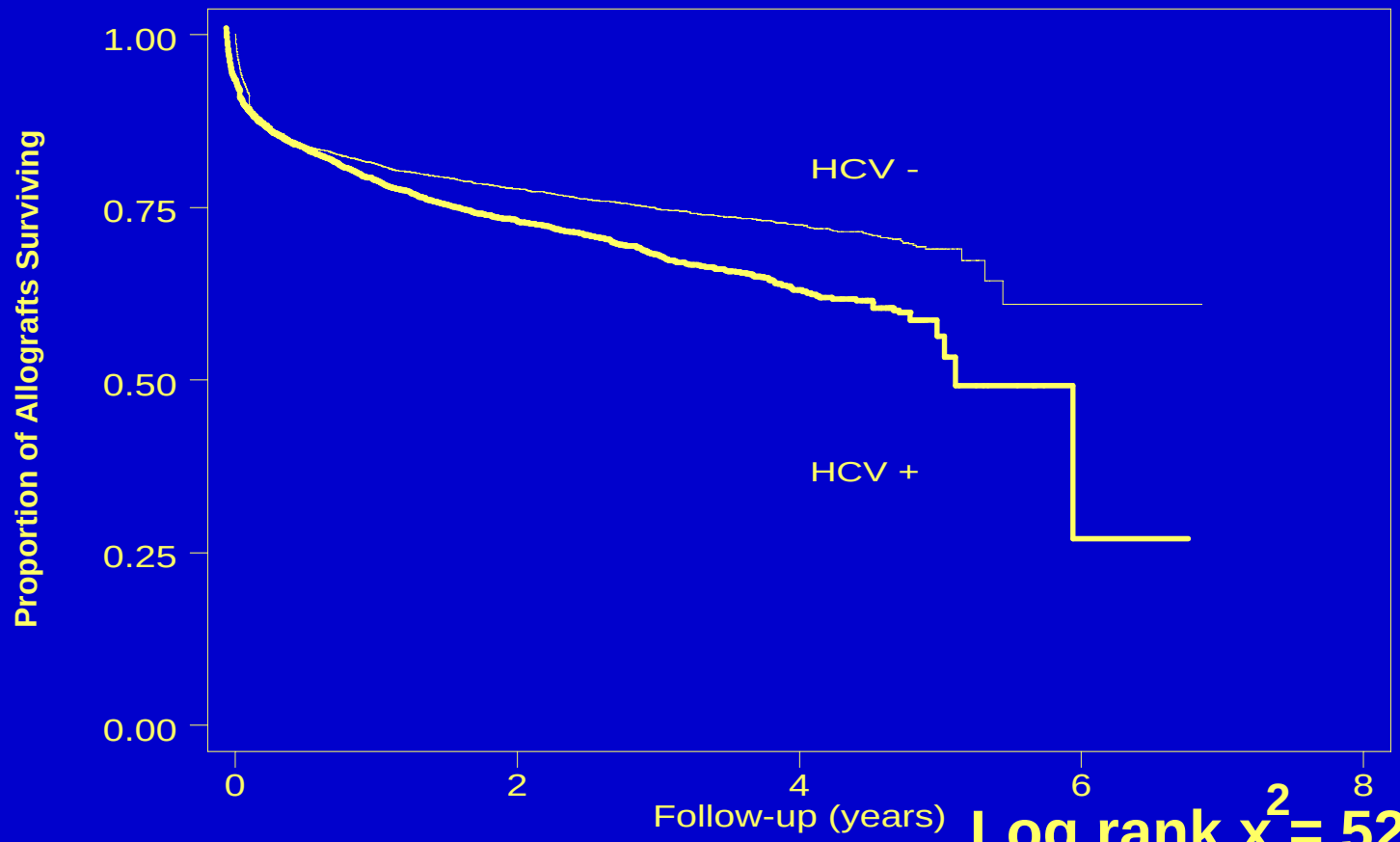
Patient Survival: HCV+ vs Others

UNOS Database. N=11,036

	1 year	5 year
Cholestatic*	91.5%	86.1%
Metabolic*	86.5%	82.4%
HBV	87.4%	78.6%
AIH	84.7%	76.8%
Cryptogenic	86.3%	73.0%
ETOH	86.7%	72.0%
HCV+	86.4%	69.9%
Malignancy*	82.5%	51.8%

*P<0.05

Allograft Survival



	1 yr	3 yr	5 yr
HCV+	76.9 %	66.4%	56.8%
HCV-	80.1%	73.3%	67.7%

Log rank x^2 = 52.85

P = 0.0001

Allograft Survival: HCV+ vs Others

	1 year	5 year
Cholestatic*	82.9%	73.4%
Metabolic*	79.2%	72.8%
AIH*	77.8%	69.5%
HBV*	81.4%	68.2%
Cryptogenic*	79.7%	65.5%
ETOH*	79.4%	64.6%
HCV+	76.9%	56.8%
Malignancy*	74.4%	46.1%

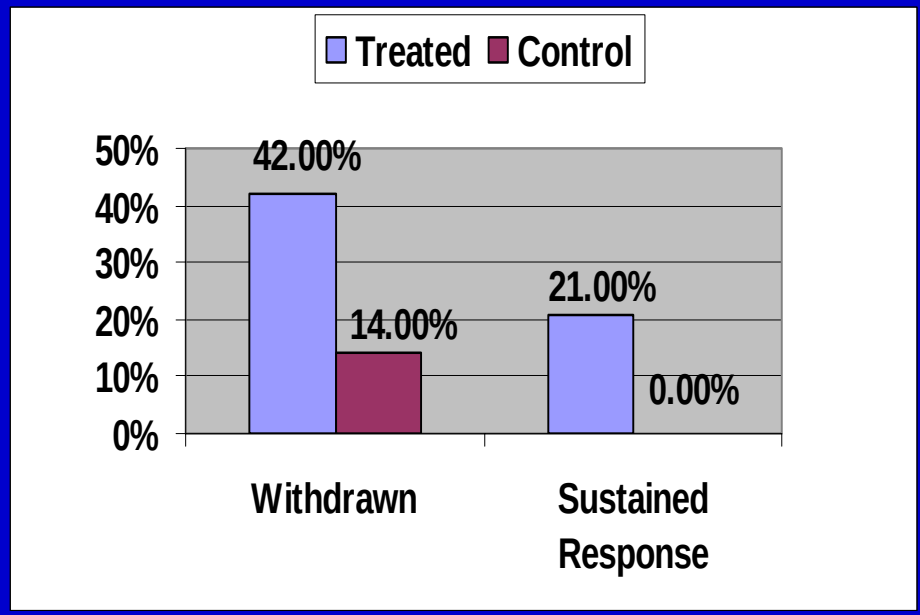
*P<0.05

Combination Antiviral Therapy Prior to Transplantation or in the Early Postoperative Period

- No good controlled studies
- Recruitment difficult
- Innovative dosage regiments: LADR
- Frequent dose reductions due to S/E
- HCV RNA levels significantly lower during interferon treatment but usual return to pretreatment levers after treatment was finished
- Occasional SRs particularly in genotype 2/3
- Effect on acute cellular rejection uncertain

Treatment of Hepatitis C After Liver Transplantation

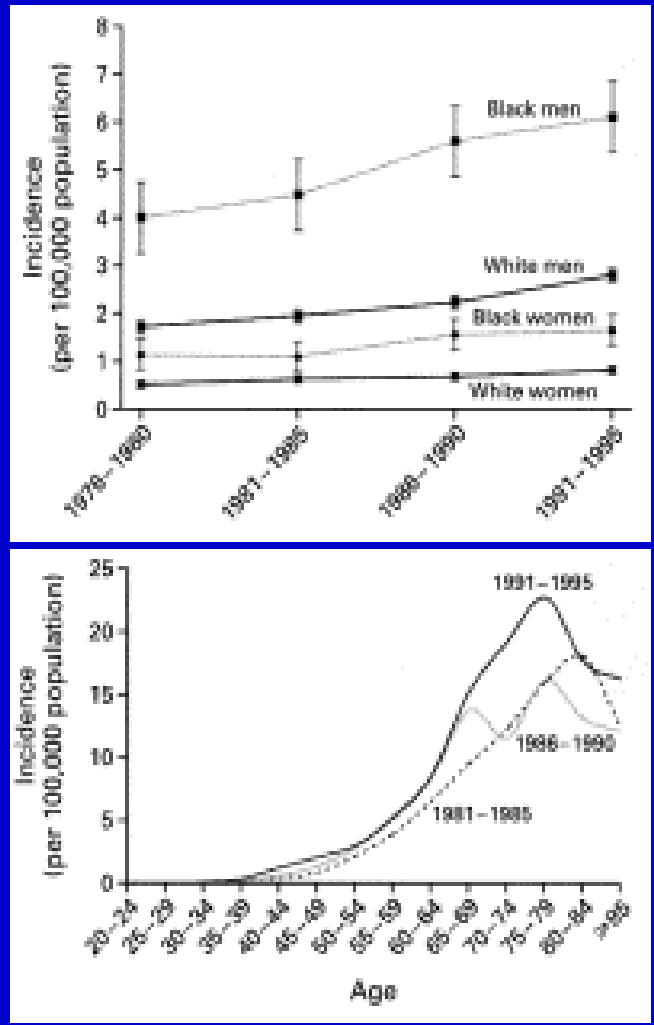
- INF alfa 2b + ribavirin for 48 wk, 24-wk follow-up
- All > 6 mo after OLT
- > 80% genotype 1
- Treated: n=28
  Control: n=24



Samuel et al. *Gastroenterology 2002*.

Changing Demographics of HCC in the US

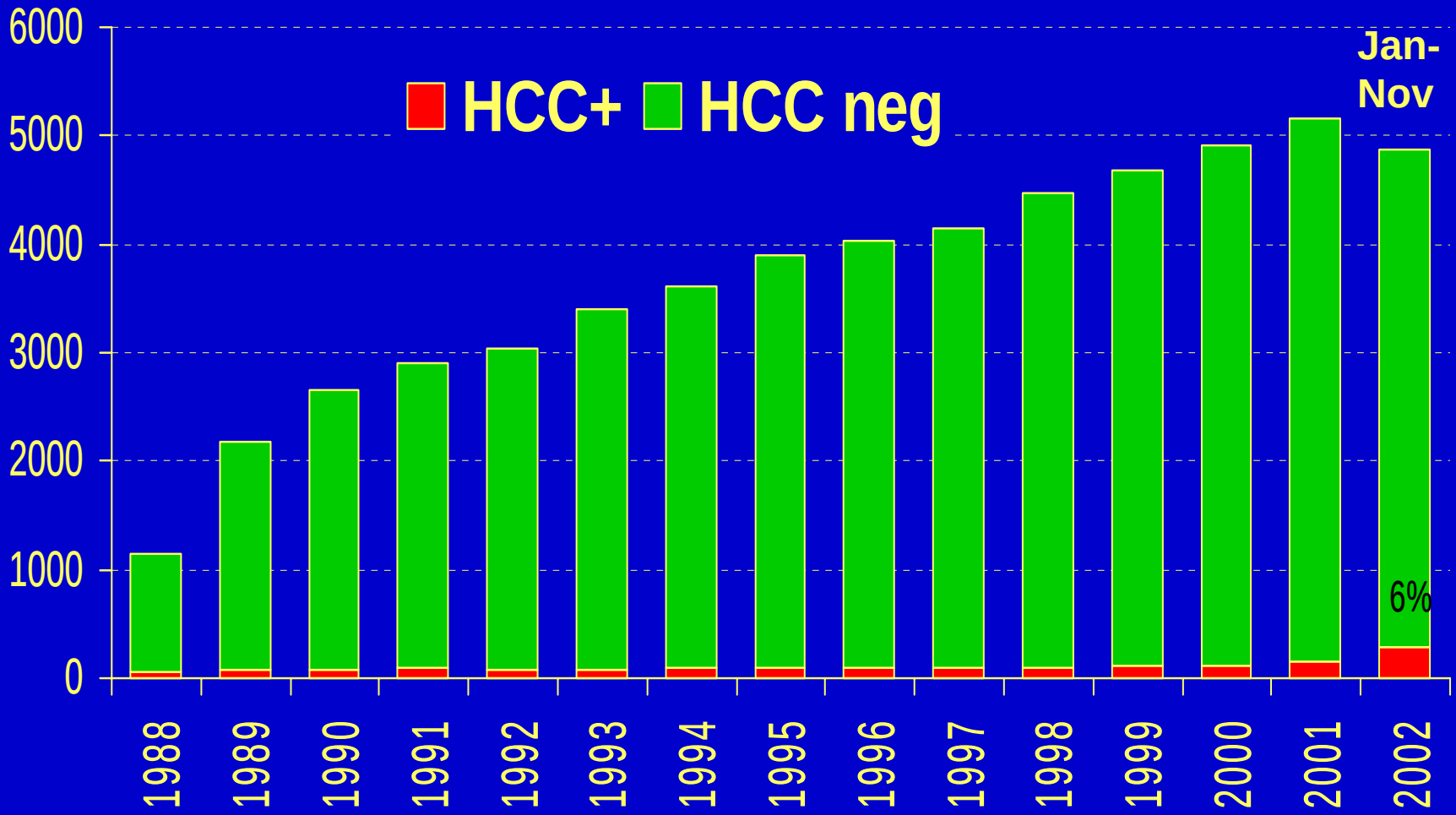
- Incidence of HCC is rising
- Mortality from HCC is rising
- Age at presentation is falling



El-Serag HB. Mason AC. *N Engl J Med 1999; 340: 745-50*

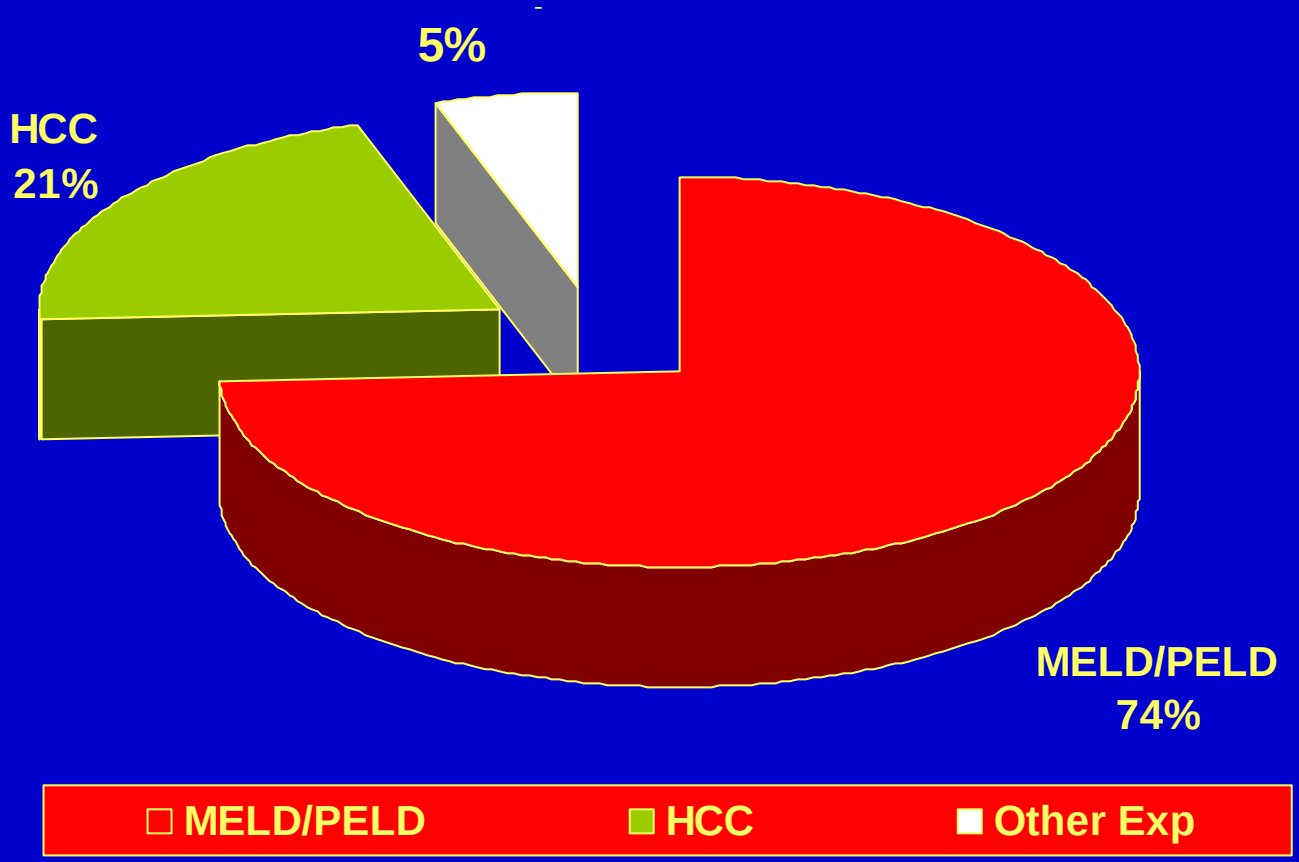
Liver Transplantation for HCC

U.S. Liver Transplants 1988-2002
(n=55,657)



OPTN,2003

Routine vs. Exceptional Cases in the MELD/PELD Era



NAFLD, NASH and Orthotopic Liver Transplantation (OLT)

- Charlton et al estimated that 3% OLTs were for NASH-cirrhosis
- 3% of 5329 = 160 OLT's
- 378 for cryptogenic cirrhosis in 2002
- NASH accounts for 50% of cryptogenics undergoing liver transplantation
- Could suggest a need of 500 LT's *per annum* by 2025 for NASH associated cirrhosis

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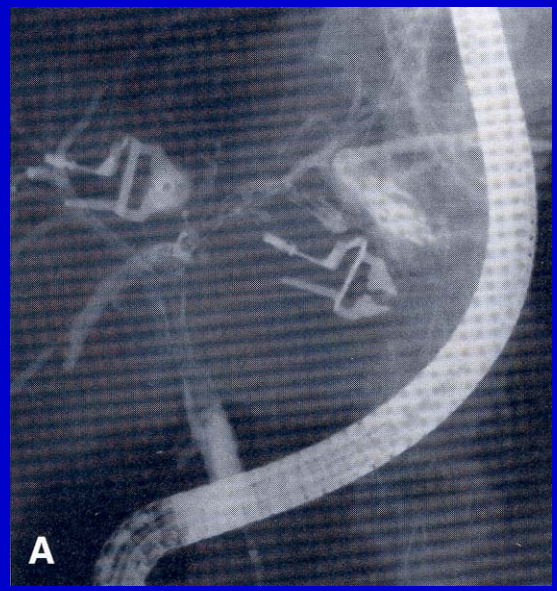
Cardiovascular Risk Factors following Liver Transplantation

Risk Factor	Prevalence Post-transplant	Rate in US Population
Hypertension (BP > 140/90)	41- 81%	15.7%
Hypercholesterolemia (>240mg%) HDL < 35mg%	20- 66% 52%	14.9% 12%
Diabetes Mellitus	21- 32%	6.2%
Obesity (BMI > 30)	39- 43%	16.1%

New Syndromes after Liver Transplantation

- Biliary Casts



- HAT/Biloma
- De Novo autoimmune hepatitis

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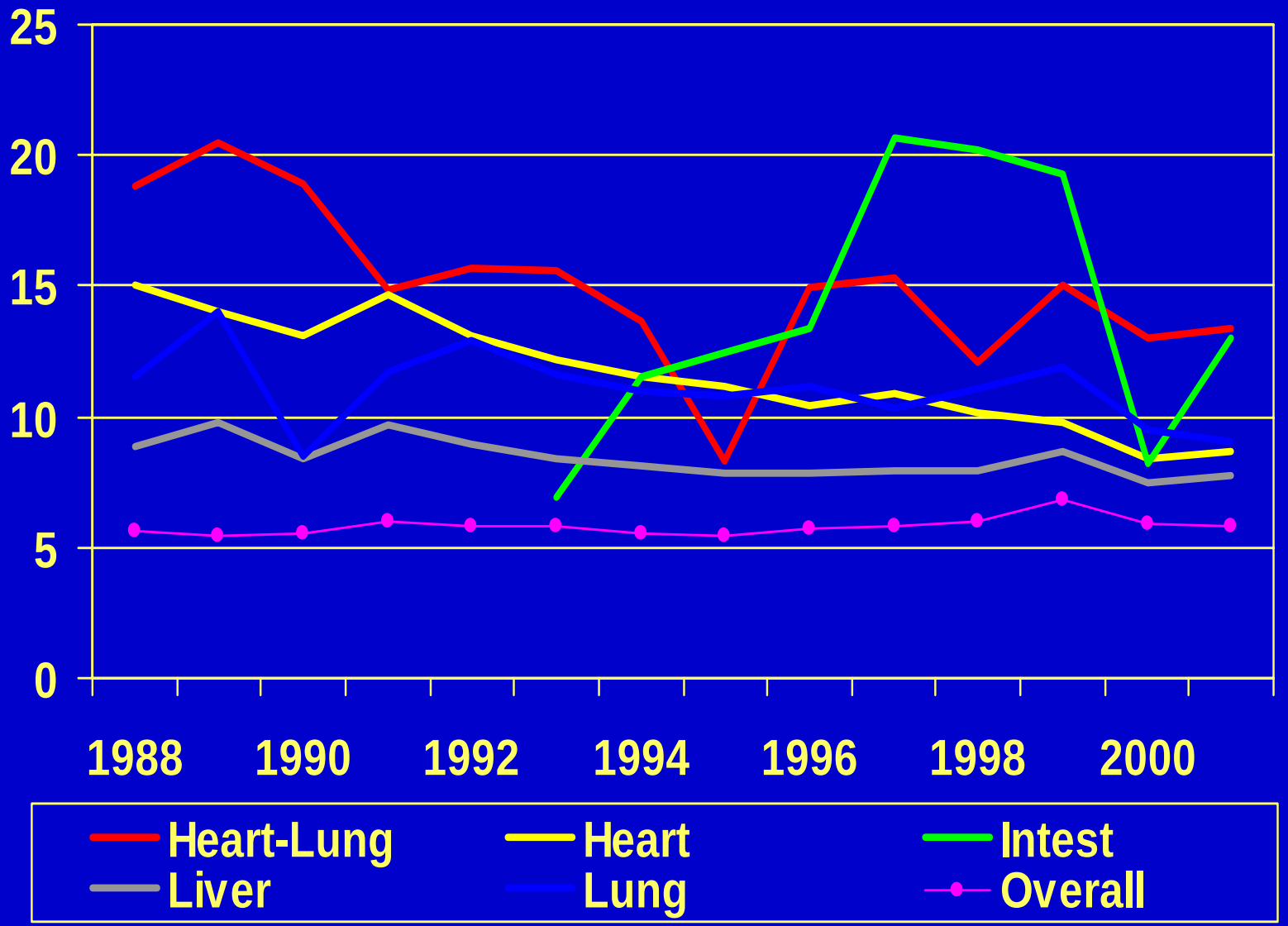
The Most Important Non-immune Problems

- Inability to determine whether a potential donor liver will be functional
- Recurrence of the original disease
  - chronic HCV: long-term consequences include fibrogenesis and the development of cirrhosis in the allograft
  - Difficulty in distinguishing the histologic HCV and cellular rejection
  - Difficulty in applying the available anti-virals in the post liver transplant setting

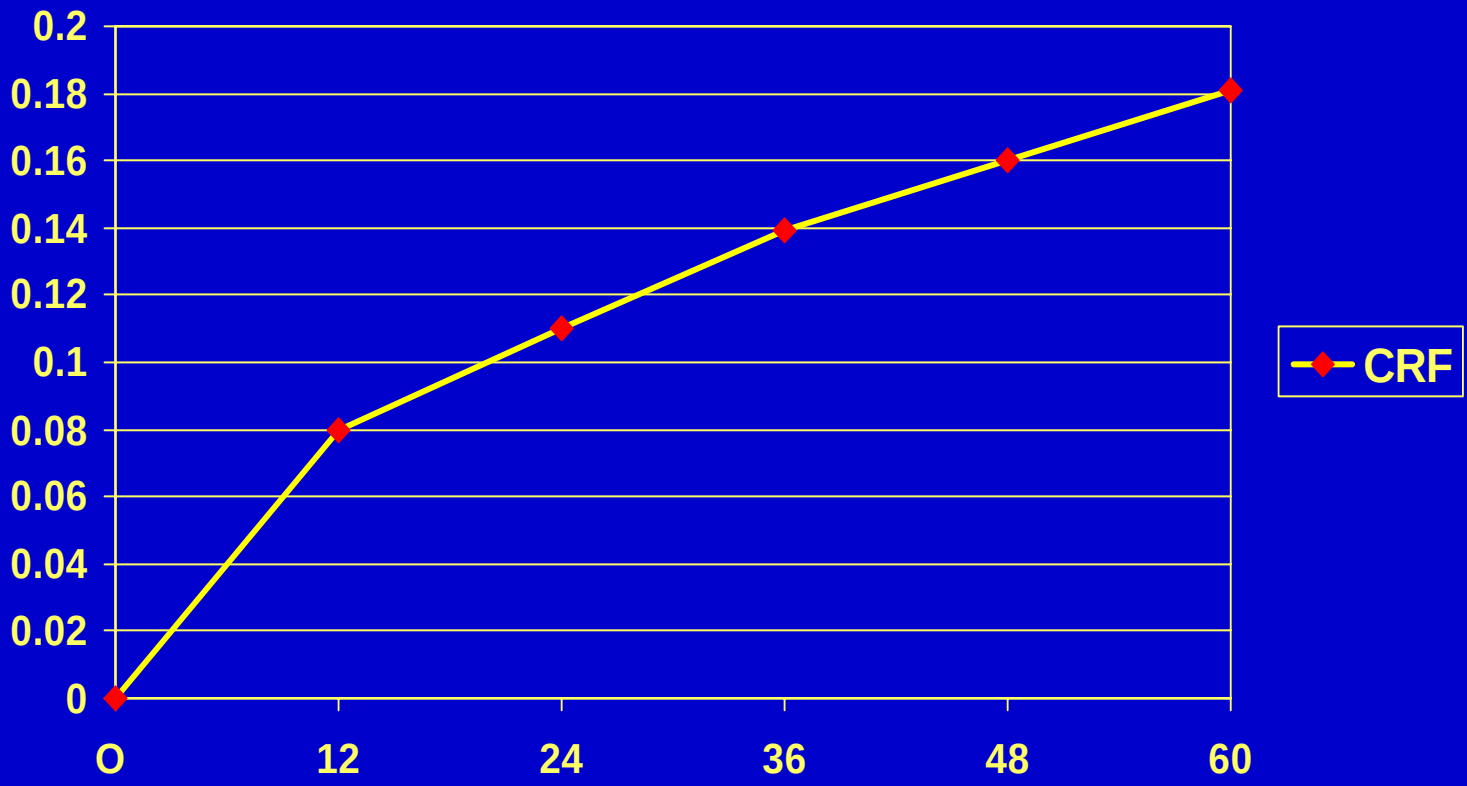
The Most Important Immune Problems

- Failure to recognize the partially tolerant state of the liver transplant
  - Excessive immunosuppression
  - Consequences of excessive immunosuppression include: diabetes, chronic renal failure, hypertension, atherosclerotic disease, osteoporosis, chronic infections and an increased incidence of cancer
- Recurrence of autoimmune diseases in allograft

DEATH RATES ON THE WAITING LIST: 1988 – 2001



Cumulative Incidence of Chronic Renal Failure in Liver Transplant Recipients



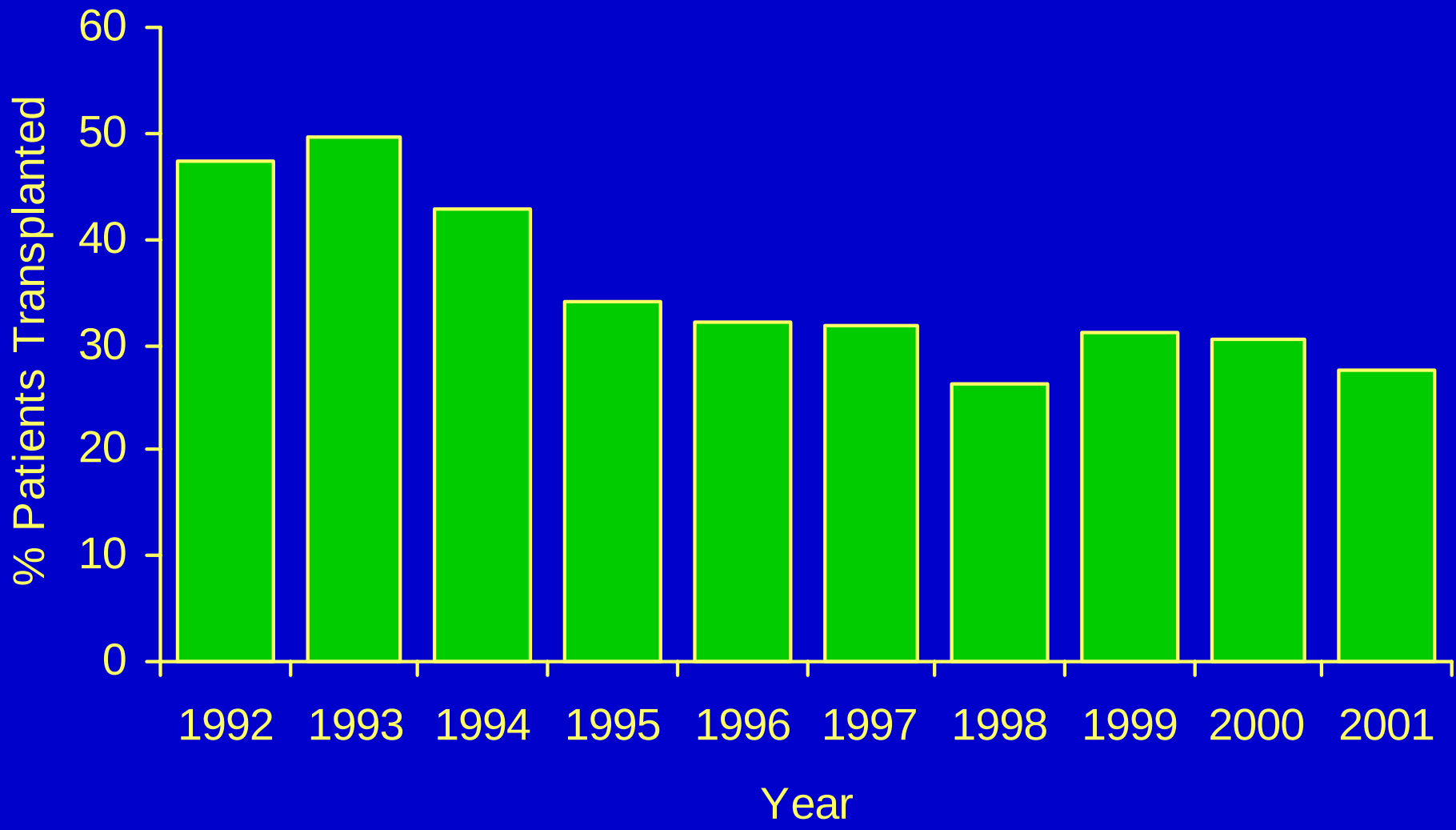
No at Risk =	36,849	28,495	24,041	19,508	15,724	12,564

OJO et al. N Engl J Med 2003; 349. 931-940

Acute Cellular Rejection

- 50% of liver transplant recipients have at least one rejection episode
- 80% of acute cellular rejection episodes occur in the first 10 weeks after transplantation
- Rejection is usually mild, controlled without additional therapy or bolus corticosteroids only
- A single episode of mild rejection may confer a survival benefit

Trends in Incidence of Rejection at 1 Year in Liver Transplant Recipients, 1992-2001



Source: *2003 OPTN/SRTR Annual Report,* Table 9.6d.

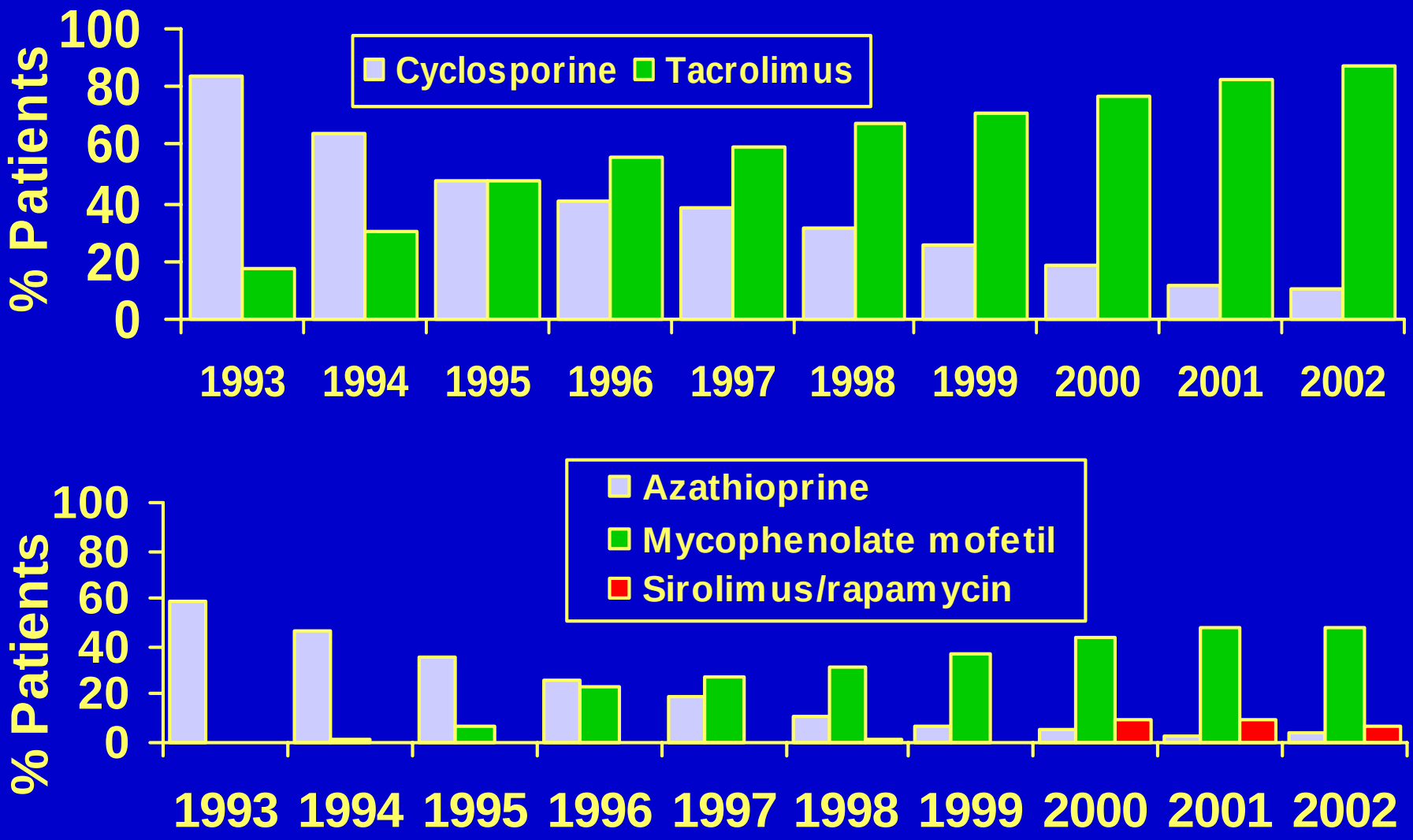
Liver Transplant Patients

- Require less immunosuppression than other solid organ recipients
- Immunosuppression declines quickly in the first few months after transplantation
- No or low corticosteroids by 3- 6 months
- Often on one agent only, usually calcineurin inhibitor
- 20 % of long-term survivors, in special circumstances, may tolerate withdrawal of all immunosuppression

Basis for Treatment Selection

- No widely agreed immunosuppressive protocols
- All liver transplant immunosuppression begins with combination therapy
- Calcineurin inhibition (CI) is almost invariable
- Most receive corticosteroids and an anti-metobolyte
- Merits of azathioprine v. MMF not proven
- Anti-IL2 R monoclonals induction in renal failure
- A few selected patients receive sirolimus

Liver Transplant Maintenance Immunosuppression Prior to Discharge, 1993-2002



Source: *2003 OPTN/SRTR Annual Report*

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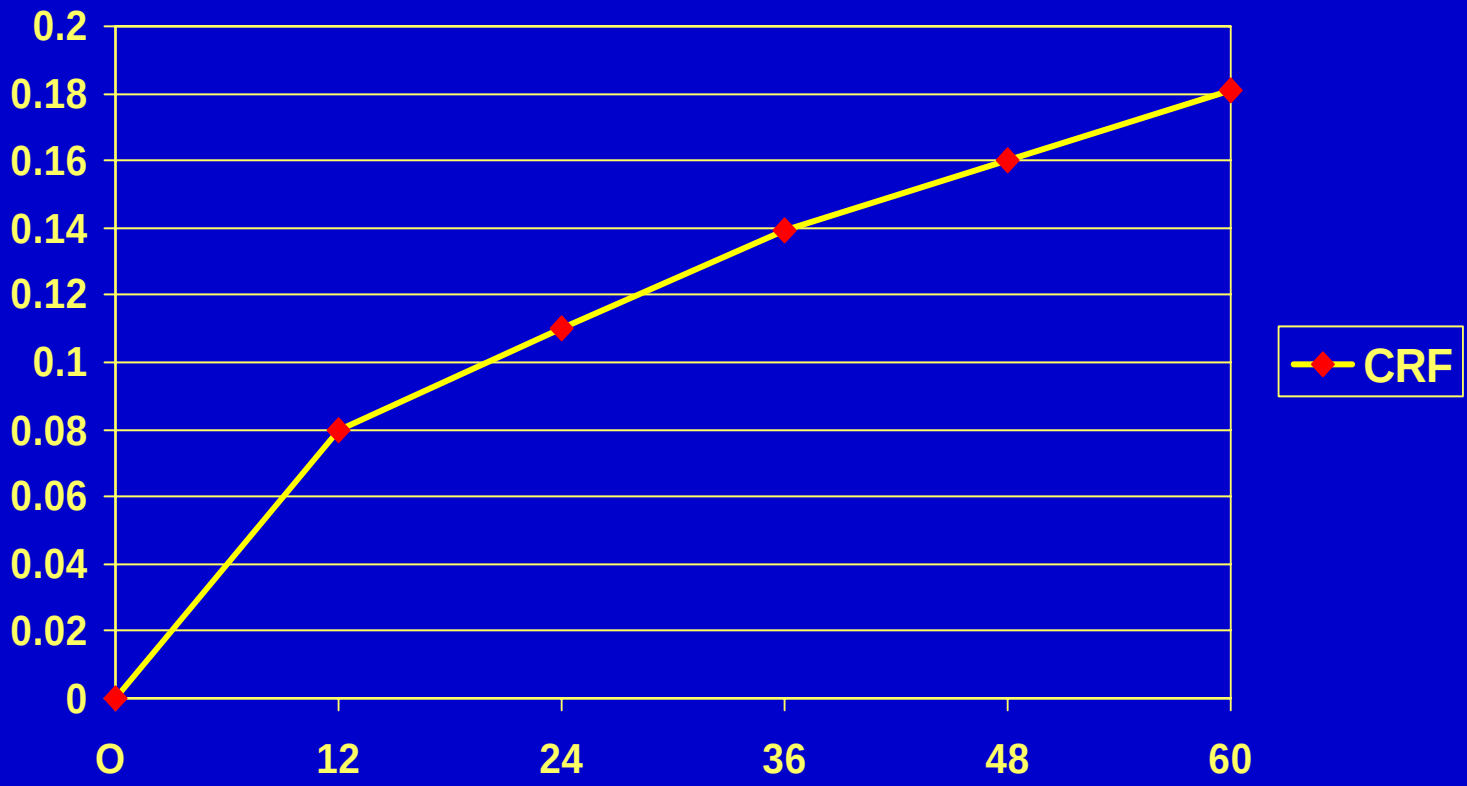

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